ORGANIC LETTERS

2005
Vol. 7, No. 24
5421−5424

Surprisingly Efficient Catalytic Cr-Mediated Coupling Reactions

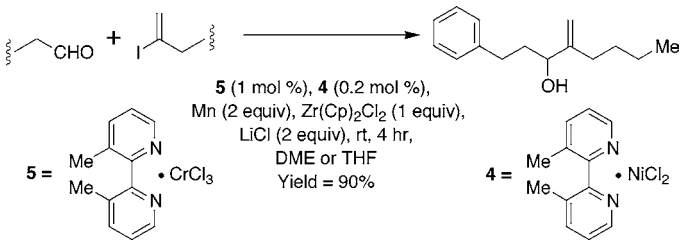
Kosuke Namba, Jiashi Wang, Sheng Cui, and Yoshito Kishi*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

kishi@chemistry.harvard.edu

Received August 30, 2005

ABSTRACT



With use of 1 mol % of Cr catalyst 5, surprisingly efficient Cr-mediated couplings of aldehydes with various types of nucleophiles have been realized. The catalyst set of Cr catalyst 5 and Ni catalyst 4 is used for alkenylation, alkynylation, and arylation, whereas the catalyst set of Cr catalyst 5 and CoPc (cobalt phthalocyanine) is used for 2-haloallylation, alkylation, and propargylation. Only the Cr catalyst 5 is required for allylation. The reaction rates in DME and THF have been found significantly faster than that in MeCN.

In the preceding paper,[1] we reported two different types of reactivity observed for the Ni catalysts used in the Ni/Cr-mediated coupling reaction. With 2,9-dimethylphenanthroline/$NiCl_2$ complex, a representative of type-I Ni catalysts, the degree of asymmetric induction in the catalytic Ni/Cr-mediated coupling in the presence of a chiral sulfonamide ligand in MeCN is equal to, or at least close to, that obtained in the stoichiometric procedure. In contrast, with 3,3′-dimethyl-2,2′-dipyridyl/$NiCl_2$ complex, a type-II Ni catalyst, the degree of asymmetric induction is significantly lower than that obtained in the stoichiometric procedure. Based on the experimental observations, we suggested that the reduction in the asymmetric induction observed for type-II Ni catalysts is due to the C−C bond formation taking place, at least partially, through a Cr complex formed with the achiral Ni ligand via a scrambling process. This analysis immediately suggests a possibility that the ligands composed of type-II Ni catalysts could facilitate catalytic Cr-mediated coupling reactions.

The feasibility of this possibility was first tested for the Ni/Cr-mediated coupling of the aldehyde **1** with the vinyl iodide **2**. To our delight, in the presence of the $NiCl_2$ complex **4** (0.5 mol %) and the $CrCl_3$ complex **5** (5 mol %), the coupling proceeded smoothly to furnish the desired allylic alcohol **3** in 90% yield. Clean couplings were observed in both DME and MeCN,[2] but the rate of coupling in DME was significantly faster than that in MeCN. The faster rate of coupling provides several obvious advantages, one of which is the possibility of lowering catalyst loadings. Indeed, with 0.2 mol % of the Ni catalyst **4** and 1 mol % of the Cr catalyst **5**, the coupling of **1** with **2** was completed within 4 h at room temperature in DME to give **3** in 90% yield. Based on these observations, we chose DME as the solvent for the following studies.

There were a number of interesting and intriguing questions surrounding this successful experiment. First, we were curious whether this new coupling reaction takes place through the steps known for the traditional Ni/Cr-mediated coupling.[3−6] To address this question, we conducted a series of experiments, including (1) an attempted coupling in the absence of the Ni catalyst **4** and (2) an attempted coupling in the absence of the Cr catalyst **5**. As anticipated, no

(1) Namba, K.; Cui, S.; Wang, J.; Kishi, Y. *Org. Lett.* **2005**, *7*, 5417.

(2) Both DME and THF were found to be excellent solvents. However, the coupling rate in DME appeared to be slightly faster than that in THF.

10.1021/ol052085k CCC: $30.25
Published on Web 10/26/2005

coupling was observed in the absence of either Ni or Cr catalyst. Interestingly, however, in the absence of the Ni catalyst **4**, both **1** and **2** were recovered unchanged, whereas, in the absence of Cr catalyst, $[Me(CH_2)_3C(=CH_2)]_2$, the homodimer of **2**, was obtained nearly quantitatively, along with the intact aldehyde **1**. These observations indicate that this process involves an oxidative addition of **2** and Ni(0) generated in situ via reduction of **4**. In the experiments summarized in Figure 1, 2 equiv of the vinyl iodide **2** was

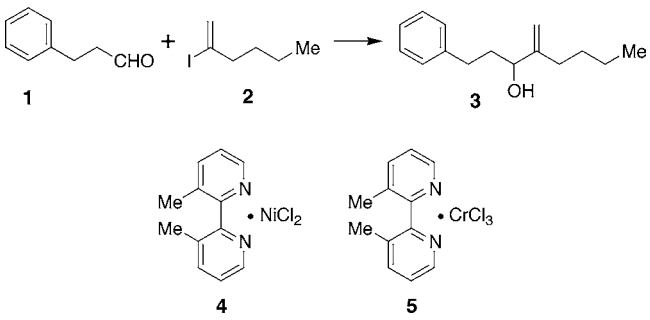


Figure 1. Ni/Cr-mediated coupling of the aldehyde **1** (1.0 equiv) and the vinyl iodide **2** (2.0 equiv) with Ni catalyst **4** and Cr catalyst **5**.

used, the excess of which resulted in formation of the homodimer. In contrast, no significant amount of the homodimer was detected in the coupling reaction with 0.7 equiv of the vinyl iodide **2** in the presence of **4** (1 mol %) and **5** (5 mol %), thereby indicating that the new catalytic reaction involves the oxidative addition of Ni(0) to a vinyl iodide, but no vinyl-Ni intermediate is accumulated; i.e., the rate of transmetalation is faster than the rate of homocoupling.

It is therefore clear that, like the traditional Ni/Cr-mediated coupling, this system also contains two catalytic cycles, one a Ni-catalyst cycle and the other a Cr-catalyst cycle. Thus, to achieve high overall efficiency for this catalytic system, it is essential to have an effective catalytic cycle for both of them. For the cycle of the Cr catalyst to continue, an agent is required to dissociate a chromium alkoxide **iv** and regenerate the Cr catalyst. TMSCl and $Zr(Cp)_2Cl_2$, both known as effective dissociation agents,[7,8] were tested in terms of their overall catalytic efficiency. Both of the dissociating agents are effective, but the overall efficiency is significantly better with $Zr(Cp)_2Cl_2$.

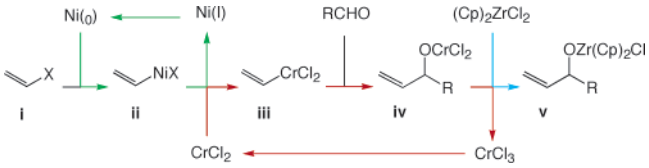


Figure 2. Ni- and Cr-catalytic cycles involved in the Ni/Cr-mediated coupling. The dissociation step is illustrated with $Zr(Cp)_2Cl_2$, which can be replaced with TMSCl.

We next investigated ligand effects on the overall catalytic efficiency. In the system described above, we used 3,3′-dimethyl-2,2′-dipyridyl (**6a**) as the common ligand for both Ni and Cr catalysts. Additional dipyridyls **6b**−**d**, as well as structurally related phenanthrolines **7a**,**b**, were also screened (Figure 3). For this screening, the catalysts were prepared

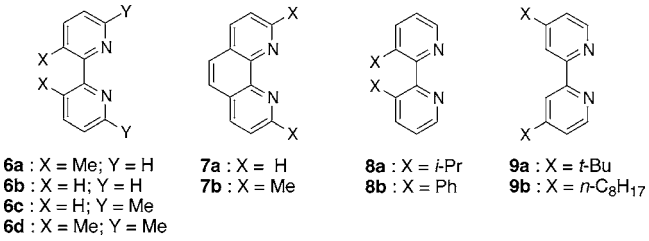


Figure 3. Dipyridyls and phenanthrolines used for preparation of Ni and Cr catalysts.

in situ from $CrCl_2$ doped with $NiCl_2$ (10%) and with each ligand;[9] the relative rate and coupling yield were used to judge their overall effectiveness.

The catalyst set prepared in situ from phenanthroline **7a** did not facilitate the coupling of **1** + **2** → **3**, whereas the catalyst set prepared from phenanthroline **7b** exhibited detectable but very poor catalytic activity. Interestingly, on addition of the Cr catalyst **5**, the catalyst set prepared from **7a** smoothly facilitated the coupling, but addition of the Ni catalyst **4** gave no effect. These results indicated that phenanthroline **7a** forms an effective Ni catalyst but does not form an effective Cr catalyst.

(3) For selected reviews on Cr-mediated reactions, see: (a) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1. (c) Nozaki, H.; Takai, K. *Proc. Jpn. Acad.* **2000**, *76*, 123. (d) Saccomano, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 173.

(4) (a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

(5) For the catalytic asymmetric Ni/Cr-mediated coupling reactions from this laboratory, see: (a) Wan, Z.-K.; Choi, H.-W.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431. (b) Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435. (c) Choi, H.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C. *Pure Appl. Chem.* **2003**, *75*, 1.

(6) For the catalytic asymmetric Ni/Cr-mediated coupling reactions from other laboratories, see: (a) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032. (b) Berkessel, A.; Schroeder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudoerfl, J. M. *J. Org. Chem.* **2004**, *69*, 3050. (c) Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* **2004**, *6*, 1293.

(7) (a) Fürstner, A.: Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.

(8) Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.

(9) For preparations and characterizations of Ni complexes relevant to this study, see: Brewer, B.; Brooks, N. R.; Abdul-Halim, S.; Sykes, A. G. *J. Chem. Crystallogr.* **2003**, *33*, 651 and references therein.

The catalysts derived from dipyridyls **6b**−**d** gave the coupling product. The effectiveness of these catalyst sets is approximately **6a** ≫ **6c** > **6d** ≈ **6b**. Interestingly, on addition of **7a**−$NiCl_2$ to the Cr catalyst prepared in situ from **6c** or **6d**, the rate of coupling was significantly accelerated, thereby indicating that the N catalyst derived from **6c** or **6d** has a poor reactivity at the step from **i** → **ii** or **ii** → **iii** or at both steps (Figure 2). However, this poor reactivity appears to be associated with the transmetalation step, because both of the Ni catalysts formed from **6c**,**d** still facilitate the homocoupling of **2**.

Through these experiments, we have recognized a structural characteristic common for effective Cr and Ni catalysts. An effective Cr catalyst has two twistable ligation sites. Despite a different degree of effectiveness, dipyridyls **6a**−**d** and **8a**,**b** afford an effective Cr catalyst. In contrary, phenanthrolines **7a**,**b**, bearing two nontwistable ligation sites, do not yield an effective Cr catalyst. However, both phenanthrolines **7a**,**b** afford an effective Ni catalyst, thereby indicating that an effective Ni catalyst is structurally represented by the tetrahedral or square-planar coordination known for the $NiCl_2$−**7a**,**b** complexes.[10] Our results suggest that an effective Cr catalyst, which plays a central role in the C−C bond-formation step, is distinctly different, or deviates, from the tetrahedral or square-planar structure. One of the dipyridyl/$CrCl_3$ complexes yielded a single crystal, the X-ray analysis of which revealed that this complex possesses an almost perfect octahedral structure (Figure 4).

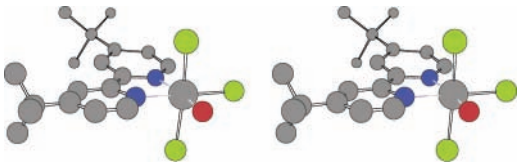


Figure 4. X-ray structure of **9a**/$CrCl_3$/H_2O, with the red ball representing the oxygen of water.

Interestingly, this complex structure is very similar to the complex structures reported from this laboratory.[5,11,12] Overall, due to the twistability along the C2−C2′ bond, dipyridyls can adopt two distinct coordination structures, thereby affording both effective Ni and Cr catalysts. Clearly, more experiments are needed to define further the static and dynamic natures of the proposed coordination structures.

Based on this structural analysis, we anticipated that other dipyridyl-based ligands would also be effective Cr and Ni catalysts. Indeed, dipyridyls **8a**,**b** and **9a**,**b** gave effective Ni and Cr catalysts. Among them, the catalysts derived from **9a** show an overall performance close to that of **4** and **5**. However, we would still recommend the catalyst set of **4** and **5** as the first choice. In our search, 3,3′-dimethyl-2,2′-dipyridyl (**6a**) is not commercially available, but 4,4′-di-*tert*-butyl-2,2′-dipyridyl (**9a**) is. Thus, for cost-effectiveness, we would suggest this set as an alternative.

We then tested other types of nucleophiles for the Ni/Cr-mediated coupling reaction (Figure 5, Ni/Cr-mediated couplings), thereby demonstrating that the applicability of the new catalytic method is excellent.[4−6,13,14]

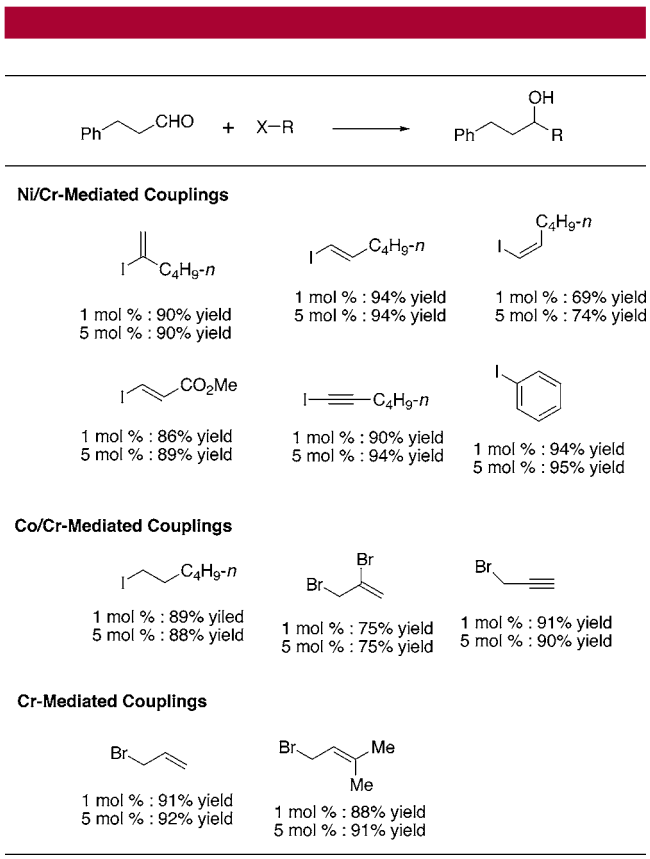


Figure 5. Representative examples tested for the new catalytic Cr-mediated coupling reactions.[13,16,19]

We studied the Co/Cr-mediated coupling reaction in the presence of the Cr catalyst **5** (Figure 5, Co/Cr-mediated

(10) For X-ray structures of Ni(II)−(1,10-phenanthroline) and Ni(II)−(2,9-dimethyl-1,10-phenanthroline), see, for example: (a) Liu, H.; Liu, L.; Zhong, B. *X-ray Struct. Anal. Online* **2004**, *20*, X63. (b) Pallenberg, A. J.; Marschner, T. M.; Barnhart, D. M. *Polyhedron* **1997**, *16*, 2711. (c) Allan, J. R.; McCloy, B. *Thermochim. Acta* **1993**, *214*, 219. (d) Butcher, R. J.; O'Connor, C. J.; Sinn, E. *Inorg. Chem.* **1979**, *18*, 492.

(11) For X-ray structures of Cr(III)−dipyridine complexes, see: Munoz, M. C.; Julve, M.; Lloret, F.; Faus, J.; Andruh, M. *J. Chem. Soc., Dalton Trans.* **1998**, *18*, 3125.

(12) For X-ray structures of [CrCl(edda or eddp)(1,10-phenanthroline)] and [$CrCl_3$(dmf)(1,10-phenanthroline)], see: (a) Yonemura, T.; Nakayama, R.; Sakagami, N.; Okamoto, K.; Ama, T.; Kawaguchi, H.; Yasui, T. *Chem. Lett.* **1998**, *3*, 215. (b) Broomhead, J. A.; Evans, J.; Grumley, W. D.; Sterns, M. *J. Chem. Soc., Dalton Trans.* **1977**, *2*, 73.

(13) The typical procedure for the catalytic Ni/Cr-mediated coupling is given below. To a suspension of **5** (0.8 mg, 0.0020 mmol), **4** (0.3 mg, 0.0010 mmol), LiCl (17 mg, 0.40 mmol), manganese powder (22 mg, 0.40 mmol), and $Zr(Cp)_2Cl_2$ (58 mg, 0.20 mmol) in DME (0.30 mL) were added **1** (27 μL, 0.20 mmol) and **2** (84 mg, 0.4 mmol). The mixture was stirred for 4 h at room temperature under nitrogen, diluted with ethyl acetate (10 mL), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with hexanes/ethyl acetate = 19/1 to 9/1) to give **3** (39 mg, 90%) as colorless oil. The molar ratio of Cr over Ni catalysts was 5/1 for all of the substrates listed under the Ni/Cr-mediated couplings, except *cis*-iodoolefin (molar ratio = 5/2) and iodoacetylene (molar ratio = 200/1). For preparation of the catalysts **4** and **5** and the single crystal of **9a**/$CrCl_3$/H_2O (Figure 4), see ref 22.

couplings).[15−17] In this series, instead of the Ni catalyst **4**, cobalt phthalocyanine (CoPc) or iron tris(2,2,6,6-tetramethyl-3,5-heptanedione) ($Fe(TMHD)_3$) was used as an activator. Between the two catalysts, CoPc was found to be slightly superior to $Fe(TMHD)_3$ in terms of the cleanliness of couplings. It is worth noting that, contrary to the examples known in the literature,[18] no allene contaminant was detected in the coupling product with propargyl bromide.

Last, the Cr catalyst **5** was tested for the third subgroup of Cr-mediated coupling reactions.[19,20] As seen from the two examples shown under the Cr-mediated couplings in Figure 5, the Cr catalyst **5** was found to be effective for the allylation subgroup as well.

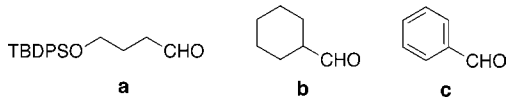
In conclusion, a new method has been developed for catalytic Cr-mediated coupling reactions. This method has excellent applicability for all three of the subgroups of Cr-mediated coupling reactions (Figure 5). The catalyst load realized in this system is at least 5−10 times better than other catalytic systems known for the Cr-mediated coupling reactions[5,6,15] or 200−400 times better than the corresponding stoichiometric procedures.[4,14,18] Furthermore, this level of catalyst-load is comparable or better than many of the catalytic C−C bond-forming reactions known in the literature.[21] Interestingly, for many of the substrates, no significant differences in chemical yields were noticed between the 1 and 5 mol % catalyst-loading experiments (Figure 5), thereby suggesting a possibility of lowering catalyst-loadings even further. The method reported here suggests several new directions for expanding the scope of Cr-mediated coupling reactions. Among them, we have recently extended this method to catalytic Ni/Cr-mediated macrocyclization without use of high dilution techniques.[22] In addition, with a suitable chiral dipyridyl ligand, we expect this method to be extended to a catalytic asymmetric process. On this front, we are currently engaged with design and development of chiral dipyridyl ligands, based on the knowledge gained from the Ni and Cr catalysts **4** and **5**.[23]

Acknowledgment. We are grateful to the National Institutes of Health (CA 22215) and Eisai Research Institute for financial support.

Supporting Information Available: X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052085K

(14) Three additional aldehydes **a**−**c** were tested under the same conditions, where **a** and **b** gave equally good results, but the coupling rate with **c** was much slower.



a **b** **c**

(15) For stoichiometric Fe- or Co/Cr-mediated alkylation, see: Takai, K.; Nitta, K.; Fujimura, O.; Utimoto, K. *J. Org. Chem.* **1989**, *54*, 4732.

(16) For catalytic Co- or Fe/Cr-mediated haloallylation, see: Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.

(17) The typical procedure for the catalytic Co/Cr-mediated coupling is given below. To a suspension of **5** (0.8 mg, 0.0020 mmol), CoPc (0.3 mg, 0.00053 mmol), LiCl (17 mg, 0.4 mmol), manganese powder (22 mg, 0.4 mmol), and $Zr(Cp)_2Cl_2$ (58 mg, 2.0 mmol) in DME (0.25 mL) were added **1** (27 μL, 0.2 mmol) and 1-iodohexane (85 mg, 0.4 mmol). The mixture was stirred for 6 h at room temperature, diluted with ethyl acetate (10 mL), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with hexanes/ethyl acetate = 19/1 to 9/1) to give 2-butyl-5-phenylpent-1-en-3-ol (39 mg, 89%) as a colorless oil.

(18) For Cr-mediated propargylation, see: (a) Inoue, M.; Nakada, M. *Organic Lett.* **2004**, *6*, 2977. (b) Wipf, P.; Lim, S. *J. Chem. Soc., Chem. Commun.* **1993**, *21*, 1654. (c) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561 (d) Place, P.; Verniere, C.; Gore, J. *Tetrahedron* **1981**, *37*, 1359.

(19) For stoichiometric Cr-mediated allylation, see: Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, *43*, 3829. For Cr-mediated catalytic asymmetric allylations, see: (a) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322. (b) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Morganti, S.; Umani-Ronchi, A. *Org. Lett.* **2001**, *3*, 1153. (c) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2327. (d) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140. (e) See ref 6a. (f) Lee, J.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837.

(20) The typical procedure for the catalytic Cr-mediated coupling is given below. To a suspension of **5** (0.8 mg, 0.0020 mmol), manganese powder (28 mg, 0.5 mmol), and $Zr(Cp)_2Cl_2$ (47 mg, 0.16 mmol) in DME (0.25 mL) were added **1** (27 μL, 0.20 mmol) and allyl bromide (43 μL, 0.50 mmol). The mixture was stirred for 2 h at room temperature, diluted with ethyl acetate (10 mL), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (elution with hexanes/ethyl acetate = 19/1 to 9/1) to give 2-butyl-5-phenylpent-1-en-3-ol (32 mg, 91%) as a colorless oil.

(21) (a) Catalyst loads used for common cross-couplings are typically in the following range: Heck coupling, 1−10 mol %; Hiyama coupling, 1−5 mol %; Kumada coupling, 0.1−3 mol %; Negishi coupling, 3−10 mol %; Sonogashira coupling, 2−10 mol % and the lowest reported is 0.0001 mol %; Stille coupling, 1−5 mol %; Suzuki−Miyaura coupling, 0.5−5 mol % and the lowest reported is 0.0001 mol %. See a review: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176 and references therein. (b) Catalyst loads used for metathesis are typically in the range of 5−10 mol %, and the lowest reported is 1 mol %. See a review: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490 and references therein.

(22) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, in press.

(23) **Preparation of the Catalyst 5.** A mixture of **6a** (300 mg, 1.6 mmol) and $CrCl_3$−3THF (411 mg, 1.1 mmol) in MeCN (10 mL) was heated until the color of the solution was changed from light purple to dark green. Then, the vapor diffusion technique was applied: the MeCN solution in an open vial was placed in a closed Et_2O chamber for 24 h to give deep green crystalline solid. The supernatant was discarded, and the crystalline solid was washed with Et_2O (×3), suspended in CH_3CN (20 mL), and heated until the solid almost completely dissolved. The resultant mixture was filtered through Celite, and the filtrate in an open vial was again placed in a closed Et_2O chamber for 24 h to give green crystals. The supernatant was discarded, and crystals were washed with Et_2O (×2) and dried under reduced pressure to give **5** (300 mg, 49%) as green crystals. **Preparation of the Catalyst 4.** A mixture of **6a** (50 mg, 0.27 mmol) and $NiCl_2$−DME (60 mg, 0.27 mmol) in MeCN (5 mL) was shaken until the suspension changed to a deep green clear solution. The mixture was concentrated under reduced pressure. The resultant solid was dried under reduced pressure to give **4** (84 mg, quant) as a deep green powder. **Preparation of the Single Crystal of 9a/$CrCl_3$/H_2O.** A mixture of **9a** (300 mg, 1.1 mmol) and $CrCl_3$−3THF (411 mg, 1.1 mmol) in MeCN (3 mL) was sonicated for 1 min, shaken until the color of the solution changed from light purple to dark green, and concentrated under reduced pressure. The residue was taken up with hot THF (50 mL). The resultant cloudy solution was filtered through Celite and concentrated down to half its volume. Then, the vapor diffusion technique was applied: the THF solution in an open vial was placed in a closed pentane chamber for 24 h to give dark green crystals. The supernatant was discarded, and the crystals were washed with pentane (×3) and dried under reduced pressure to give the Cr complex **(**300 mg, 58%). A single crystal was grown from THF−pentane. An X-ray analysis showed that this crystal contains one water molecule; see Figure 4.